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Deviant white matter structure in adults with attention-deficit/hyperactivity disorder points to aberrant myelination and affects neuropsychological performance

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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) in childhood is characterized by gray and white matter abnormalities in several brain areas. Considerably less is known about white matter microstructure in adults with ADHD and its relation with clinical symptoms and cognitive performance. In 107 adult ADHD patients and 109 gender-, age- and IQ-matched controls, we used diffusion tensor imaging (DTI) with tract-based spatial statistics (TBSS) to investigate whole-skeleton changes of fractional anisotropy (FA) and mean, axial, and radial diffusivity (MD, AD, RD). Additionally, we studied the relation of FA and MD values with symptom severity and cognitive performance on tasks measuring working memory, attention, inhibition, and delay discounting. In comparison to controls, participants with ADHD showed reduced FA in corpus callosum, bilateral corona radiata, and thalamic radiation. Higher MD and RD were found in overlapping and even more widespread areas in both hemispheres, also encompassing internal and external capsule, sagittal stratum, fornix, and superior lateral fasciculus. Values of FA and MD were not associated with symptom severity. However, within some white matter clusters that distinguished patients from controls, worse inhibition performance was associated with reduced FA and more impulsive decision making was associated with increased MD. This study shows widespread differences in white matter integrity between adults with persistent ADHD and healthy individuals. Changes in RD suggest aberrant myelination as a pathophysiological factor in persistent ADHD. The microstructural differences in adult ADHD may contribute to poor inhibition and greater impulsivity but appear to be independent of disease severity.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common childhood psychiatric disorder with an estimated prevalence around 5.3% in childhood that persists through adolescence reaching a prevalence of up to 4.9% in adults (Simon et al., 2009). ADHD is associated with global and regional brain volume reductions. Meta-analytic findings show reductions in total cerebral volume, in frontal lobes, cingulate cortex, and corpus callosum; in addition, robust evidence exists for decreased gray matter volume in subcortical areas (Ellison-Wright et al., 2008; Frodl and Skokauskas, 2012; Nakao et al., 2011; Valera et al., 2007). Differences in subcortical structures such as the putamen and caudate seem to disappear with increasing age (Castellanos et al., 2002; Nakao et al., 2011). Moreover, longitudinal studies show a delay in the age by which peak cortical thickness is reached in ADHD patients (Shaw et al., 2007), which has led to the suggesting that ADHD may be the outcome of a maturational lag that eventually normalizes (Rubia, 2007). More recent results of longitudinal studies indicate, however, that reductions in basal ganglia, which were detected in childhood, persisted into adolescence (Shaw et al., 2014). Cross-sectional studies in adults with ADHD also point to persistent gray matter reductions in subcortical volumes (Frodl et al., 2010; Onnink et al., 2014; Proal et al., 2011; Seidman et al., 2011) as well as in cortical areas (Ahrendts et al., 2011;

Abbreviations: ADHD, Attention-deficit/hyperactivity disorder; DTI, Diffusion tensor imaging; TBSS, Tract-based spatial statistics; FA, Fractional anisotropy; MD, Mean diffusivity; AD, Axial diffusivity; RD, Radial diffusivity; ROI, Region of interest; SAD, Sustained attention dots; SART, Sustained attention to response task.

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Amico et al., 2011; Biederman et al., 2008; Makris et al., 2007; Seidman et al., 2006, 2011), and in cerebellar regions (Proal et al., 2011; Seidman et al., 2011).

Over the last decade, the focus of neuroimaging research has widened from studies of regional volume alterations to studies of altered white matter connections within and among several neural networks (Konrad and Eickhoff, 2010). Advances in diffusion tensor imaging (DTI) allowed non-invasive investigation of white matter tracts connecting cortical and subcortical regions (Thomason and Thompson, 2011). DTI probes both the microstructural organization and the myelination of white matter through measuring the diffusion of water molecules in the tissue (Beaulieu, 2002; Le Bihan et al., 2001). Commonly used parameters are fractional anisotropy (FA) and mean diffusivity (MD), which reflect the preferential directionality of water diffusion along white matter tracts and the magnitude of diffusion, respectively (Le Bihan et al., 2001). Although decreased FA is a characteristic of impaired white matter integrity, its exact neurobiological meaning is not fully understood (Beaulieu, 2002).

Impaired white matter integrity has been found in numerous psychiatric disorders including major depressive disorder (Korgaonkar et al., 2011), bipolar disorder (Barysheva et al., 2013), schizophrenia (Mandl et al., 2013) and ADHD. A meta-analysis in children, adolescents, and adults with ADHD provided evidence of microstructural abnormalities in areas such as the anterior corona radiata (ACR), forceps minor, bilateral internal capsule, and cerebellum (van Ewijk et al., 2012). This meta-analysis only included hypothesis-free whole-brain voxelwise (VBA) approaches and could not provide directionality of findings (e.g., higher or lower FA in ADHD). Hypothesis-driven region of interest (ROI) studies reported that ADHD is in general associated with lower FA in the corpus callosum (Cao et al., 2010), cerebellum (Bechtel et al., 2009), and in several fronto-striatal tracts (Hamilton et al., 2008; Pavuluri et al., 2009; Shang et al., 2013; Wu et al., 2014). Some studies revealed that ADHD patients had *higher* FA (de Zeeuw et al., 2012; Silk et al., 2009; Tamm et al., 2012) in fronto-striatal regions when compared with healthy controls. A recent study found clusters of decreased FA and MD in most of the major white matter tracts and concluded that white matter alterations are a wide-ranging rather than localized feature in children and adolescents with ADHD (van Ewijk et al., 2014). Analyses using graph theory in combination with whole-brain DTI (e.g., brain connectomics) revealed similarly that, in children and adolescents with ADHD, decreased white matter connectivity in fronto-striatal circuits extended to a larger brain network which encompassed additional cortico-cortical, subcortical, and cerebellar circuits (Hong et al., 2014). The few available DTI studies of adult ADHD patients to date showed decreased FA in tracts such as the cingulum bundle (Makris et al., 2008), the inferior longitudinal fasciculus (ILF) (Konrad et al., 2012), the superior longitudinal fasciculus (SLF) (Cortese et al., 2013; Makris et al., 2008), and the corpus callosum (Dramsdahl et al., 2012). Although the current ADHD literature lacks longitudinal DTI studies, decreased FA has been reported in persistent *and* remitted adult patients with ADHD in comparison with healthy controls. These persistent findings were observed in areas including the corona radiata, sagittal stratum, the retrolenticular internal capsule, and the SLF (Cortese et al., 2013). Conversely, another study found that remitted adult patients did not differ significantly from controls, while patients with persistent ADHD had decreased FA in the uncinated and inferior fronto-occipital fasciculi (Shaw et al., 2015).

Decreased FA is typically accompanied by increased MD values in studies of ADHD. Increased MD is related with decreased cellular density (Alexander et al., 2007) and may reflect abnormalities in ADHD more sensitively than FA (de Luis-Garcia et al., 2015; Lawrence et al., 2013). Moreover, decreased FA might result from increased radial diffusivity (RD) and/or reduced axial diffusivity (AD) (Alexander et al., 2007). While the biological correlates of those measures are not yet entirely clarified, decreases in AD are currently thought to indicate axonal damage or degeneration, and increases in RD with minimal changes in AD are thought to indicate increased freedom of cross-fibre diffusion and possibly decreased myelination (Alexander et al., 2007; Song et al., 2002). Reporting changes in RD and AD could potentially help elucidate the FA findings in studies of ADHD. In the ADHD childhood literature, reports on RD have shown the entire range from increased RD (Helpern et al., 2011; Nagel et al., 2011) to decreased RD (Silk et al., 2009), and one study reported no change in RD (Tamm et al., 2012). Increased AD (together with an increased FA) has been reported in two childhood studies (Silk et al., 2009; Tamm et al., 2012). A recent study in adult ADHD patients suggested that reductions of FA were driven by changes in RD rather than AD (Shaw et al., 2015).

In addition to case–control comparisons, some studies investigated the behavioural implications of changed white matter variation in patients with ADHD by looking at its association with clinical symptoms or cognitive measures. Although findings in the ADHD literature are heterogeneous and complex, most studies have found that increasing symptom severity was associated with decreased FA (Ashtari et al., 2005; Nagel et al., 2011; Shang et al., 2013), but also with higher FA (Peterson et al., 2011; van Ewijk et al., 2014). In an adult ADHD study, attentional performance correlated with FA and MD in the right SLF, and measures of impulsivity correlated with FA in right orbitofrontal fibre tracts (Konrad et al., 2010).

Taken together, there is strong evidence for wide-spread white matter differences in ADHD patients compared to controls, and these may be related to ADHD symptomatology and cognitive functioning. Findings in the ADHD literature differ in precise location and directionality, which makes comparison of studies difficult. This is likely due to differences in sample characteristics (e.g., gender, age ranges), small sample sizes, and methodological differences (e.g., use of VBA versus ROI approaches). Relative to childhood and adolescent ADHD studies, there are few DTI studies in adult patients, and those are hampered by small sample sizes and by the use of ROIs instead of whole-brain approaches (except for the study by Cortese et al. (2013)). In adult ADHD, only few studies investigated AD and RD (Shaw et al., 2015), associations with ADHD symptomatology (Dramsdahl et al., 2012; Shaw et al., 2015), and cognitive performance (Konrad et al., 2012). Therefore, an overall picture of white matter pathology in adult ADHD is currently lacking.

In this study, we used DTI to comprehensively compare white matter variation in adults with ADHD and healthy controls. We investigated values of FA, MD, AD, and RD using tract-based spatial statistics (TBSS), which is a whole-skeleton voxel-by-voxel analysis (Smith et al., 2006). Within the ADHD group, we investigated associations of FA and MD with clinical symptom scores and cognitive measures. These cognitive measures were selected to cover prominent cognitive domains commonly affected in adults with ADHD (e.g., working memory, attention, inhibition, and delay discounting/impulsivity). Based on the current literature, we expected to find (a) widespread decreases of FA and increases of MD and RD in ADHD, and (b) associations of FA with symptom severity and cognitive performance.

2. Materials and methods

2.1. Subjects and procedure

In total, 216 individuals (107 patients with persistent ADHD, 109 healthy controls) from the Dutch cohort of the International Multicentre persistent ADHD CollaboraTion (IMpACT) (Franke et al., 2010) participated in this study. The patients and an age-, gender-, and IQ-matched group of healthy controls were recruited through the Department of Psychiatry of the Radboud University Medical Center and through advertisements.

Patients were included if they met DSM-IV-TR criteria for ADHD in childhood as well as adulthood, as assessed by a psychiatrist. At the time of inclusion into the study, participants were assessed using the Diagnostic Interview for Adult ADHD (DIVA) (Kooij, 2010). This

Table 1
Demographic, clinical, and cognitive characteristics of ADHD patients and healthy controls (HC).

	ADHD (N = 107)	HC (N = 109)	Test of significance
Gender (males/females)	41/66	47/62	$\chi2 = 0.51$, $p = .47$
Age (years)	35.00 ± 10.30	36.08 ± 10.97	t (1,214) = 0.74, $p = .46$
IQ[a]	108.13 ± 14.43	110.97 ± 15.36	t (1,214) = 1.40, $p = .16$
Inattention symptoms[b]	7.27 ± 1.56	0.59 ± 1.29	t (1,214) = −34.48, $p < .0001$
Hyperactivity/impulsivity symptoms[b]	5.65 ± 2.36	0.59 ± 1.12	t (1,214) = −19.96, $p < .0001$
Digit span[c]	6.77 ± 2.2	7.53 ± 2.38	F(1,208) = 6.56, $p < .01$
SAD[d]	3.53 ± 0.26	3.42 ± 0.19	F(1,202) = 11.94, $p < .001$
SART[e]	11.02 ± 4.76	9.29 ± 5.04	F(1,187) = 5.31, $p = .02$
Delay discounting[f]	0.038 ± 0.064	0.010 ± 0.015	F(1,187) = 16.31, $p < .0001$
DTI acquisition protocol[g]	35 (33%)	23 (21%)	$\chi2 = 3.71$, $p = .05$
One or more depressive episode(s) (remitted)[h]	52 (57%)	12 (11%)	
Anxiety disorder (remitted)[h]	22 (23%)	6 (6%)	
Substance use disorder (remitted)[h]	21 (20%)	6 (6%)	
Borderline Personality D[h]	10 (9%)	–	
Medication-naive	20 (19%)	–	
On stimulant medication	64 (60%)	–	
Medication in the past	14 (13%)	–	
On atomoxetine	9 (8%)	–	

Demographic information representing means ± standard deviations or percentage per group.
[a] Prorated from Block Design and Vocabulary of WAIS-III-R.
[b] As measured with the ADHD-DSM-IV Self Rating scale (Kooij et al., 2005).
[c] Digit Span raw backwards score (working memory).
[d] Errors Sustained Attention Dots (SAD) task (attention).
[e] Commission errors Sustained Attention to Response Task (SART) (inhibition).
[f] Score on Delay Discounting task (impulsivity).
[g] First version of DTI acquisition protocol.
[h] As measured by the Structured Clinical Interview for DSM-IV for axis I (Groenestijn et al., 1999) and axis II (Weertman et al., 2000) disorders.

interview focuses on the 18 DSM symptoms of ADHD and uses concrete and realistic examples to thoroughly investigate, whether a symptom is currently present or was present in childhood. In order to obtain information about ADHD symptoms and impairment in childhood, additional information was acquired from parent and school reports, whenever possible. The Structured Clinical Interview for DSM-IV (SCID-I & SCID-II) was used for comorbidity assessment (see Table 1). Assessments were carried out by trained professionals (psychiatrists or psychologists). In addition, a quantitative measure of clinical symptoms was obtained using the ADHD-DSM-IV Self Rating scale (Kooij et al., 2005).

Exclusion criteria for participants were psychosis, alcohol or substance use disorder in the last 6 months, current major depression, full-scale IQ estimate <70 (assessed using the Wechsler Adult Intelligence Scale-III), neurological disorders, sensorimotor disabilities, non-Caucasian ethnicity, and medication use other than psychostimulants, atomoxetine, or bupropion. An additional exclusion criterion for the healthy control subjects was a current neurological or psychiatric disorder according to SCID-I and SCID-II. This study was approved by the regional ethics committee (Centrale Commissie Mensgebonden Onderzoek: CMO Regio Arnhem—Nijmegen; Protocol number III.04.0403). Written informed consent was obtained from all participants.

2.2. Acquisition of diffusion-weighted images

Whole-brain imaging was performed with a 1.5 Tesla MR scanner (Magnetom Avanto, Siemens Medical Systems, Erlangen, Germany) and a standard 8 channel head coil. A 3D T1-weighted MPRAGE anatomical scan was obtained from each subject (Repetition Time (TR) = 2730 ms, Echo Time (TE) = 2.95 ms, Inversion Time (TI) = 1000 ms, flip angle = 7°, field of view = 256 × 256 × 176 mm^3, voxel size = 1.0 × 1.0 × 1.0 mm^3). The T1 images served as high resolution anatomical reference image for diffusion imaging data. Transversely oriented diffusion-weighted images were acquired using a twice-refocused spin-echo-planar-imaging sequence that minimized imaging distortions from eddy currents (Reese et al., 2003). The diffusion imaging data were acquired using two different protocols. Fifty-eight subjects were scanned with the following protocol: TR = 10200 ms, TE = 95 ms, field of view = 320 × 320 × 160 mm^3, voxel size = 2.5 × 2.5 × 2.5 mm^3, 6/8 partial Fourier. Four images without diffusion-weighting (b = 0 s/mm^2) and 30 images with diffusion-weighting (b = 900 s/mm^2, diffusion directions = 34) applied along non-collinear directions were acquired. The remaining 158 subjects were scanned with an improved second protocol, which was implemented to reduce motion artifacts during scanning. Parameters that differed from the first protocol were TR (6700 ms), TE (85 ms), field of view (220 × 220 × 140 mm^3), and scans were acquired with full Fourier acquisition, other parameters were unchanged. For each slice, the diffusion-weighting for the 30 images changed to b = 900 s/mm^2. Acquisition protocol was included as covariate in all analyses.

2.3. Preprocessing and skeletonization of diffusion-weighted images

The diffusion-weighted data was preprocessed using an in-house developed algorithm. In short, the diffusion-weighted images of each subject were realigned on the unweighted image using mutual information routines from SPM8 (Wellcome Trust Center for Neuroimaging). Next, an iteratively reweighted-least-squares algorithm (PATCH) was used to robustly correct for head and cardiac motion artifacts in the diffusion-weighted data (Zwiers, 2010). Using DTIFIT from the FMRIB's Diffusion Toolbox (part of FMRIB's Software Library (FSL)), FA images were created and subsequently fed into the TBSS pipeline (Smith et al., 2006). Here, all individual FA maps were nonlinearly registered to the FMRIB58_FA template using FSL's nonlinear registration tool FNIRT. Then, the nonlinear transforms found in the previous stage were applied to all subjects to bring them into standard Montreal Neurological Institute (MNI) space. A mean FA image was created and thinned to create a mean FA skeleton which represents the centres of all tracts common to the group. A threshold of 0.2 was used to avoid partial voluming effects. Individual FA images were then mapped onto this skeleton resulting in a skeletonized FA image for each individual. Finally, each participant's FA, MD, AD, and RD image was projected onto this skeleton, and resulting data were used for voxel-wise statistics.

2.4. Neuropsychological assessment

Cognitive functioning of participants was assessed by a neuropsychological test battery that was composed to cover multiple cognitive domains earlier found affected in ADHD (Mostert et al., submitted for publication): (i) working memory, assessed via the WAIS-III Digit Span task (Wechsler, 1997); (ii) attention, measured with the response bias variable of the Sustained Attention Dots task (De Sonneville, 1999); (iii) inhibition, tested via the Sustained Attention to Response Task (SART) (Smit et al., 2004); and (iv) delay discounting/impulsivity assessed via the Delay Discounting task (Dom et al., 2006). Assumptions with respect to the residuals were checked and neuropsychological measures were log-transformed if necessary to achieve a normal distribution. Outliers were defined as having a score more extreme than 4-times the standard deviation above or below the mean per group. Details of task and outcome measures are described in Supplementary Table S1.

2.5. Statistical analysis

First, we performed a between-subject whole-skeleton voxel-wise analysis using TBSS, in which we compared patients to control subjects on values of FA, MD, AD, and RD. In all analyses, gender, age, and scan acquisition protocol were included in the model as nuisance regressors. Threshold-free cluster enhancement (TFCE) was applied to obtain cluster-wise statistics corrected for multiple comparisons. Briefly, this method transforms local T-statistics into TFCE statistics that reflect both the size of the local effect (or "height") and the cluster extent (Smith and Nichols, 2009). With the obtained TFCE maps, "randomize" then calculates a p-value (p-corrected) for each voxel, corrected for whole-skeleton family-wise error (FWE) rate via permutation testing (5000 permutations). The TFCE-corrected p-value maps were thresholded at $P_{FWE} = 0.05$, and we report regions that contained clusters of at least ten contiguous suprathreshold voxels. Significant results were localized to anatomical locations using the Johns Hopkins University (JHU)—ICBM-DTI-81 white matter labels atlas (Mori et al., 2008) and the white matter tractography atlas (Hua et al., 2008). To estimate the effect size of significant clusters, spatially averaged scores were calculated from significant clusters for each subject, and subsequently partial eta-squared was calculated using SPSS version 21 (IBM, Chicago, IL).

Secondly, within the ADHD group we performed two whole-skeleton regression analyses in TBSS similar to van Ewijk et al. (2014). This analysis was performed using self-reported symptom counts on both dimensions (inattention and hyperactivity/impulsivity) as two separate predictors. Gender, age, and scan acquisition protocol were included in the model as nuisance regressors. The TFCE-corrected p-value maps were thresholded at $P_{FWE} = 0.05$. In addition, two analyses were performed in the ADHD group to further investigate significant between-group findings from the first TBSS analysis in an ROI approach for their link with symptom severity. From each significant FA and MD cluster, an ROI mask was created and was then back-projected to the original images of each individual; subsequently, spatially averaged FA and MD values were obtained. Partial correlation analyses were performed (in SPSS) to identify correlations between the extracted average of FA and MD for each cluster and self-reported symptom count on both dimensions, adjusting for gender, age, and scan acquisition protocol.

Third, similar partial correlation analyses as listed above were performed (in SPSS) for the extracted average of FA and MD (for each cluster) and cognitive measures (working memory, attention, inhibition, delay discounting/impulsivity), adjusting for gender, age, and scan acquisition protocol. These partial correlation analyses were performed in the whole group. Post-hoc analyses were carried out for significant findings, in which the ADHD and control group were tested separately to explore potential group-specific effects. For the two latter analyses, Bonferroni correction was used and the p-value of 0.05 was divided by the number of significant FA and MD clusters and multiplied by two for the analysis with symptom dimensions and multiplied by four for the analysis with the four cognitive measures.

Lastly, to explore whether stimulant medication or a history of comorbid major depressive disorder, the most frequent comorbidity of ADHD in our cohort, confounded our between-group results, general linear models (GLM) were used (in SPSS). The extracted mean values from the significant between-group FA, MD, RD, and AD clusters were included as dependent factors. For the GLM of medication, healthy controls (N = 109), medication-naive patients (N = 20), and patients using stimulant treatment (N = 64) were added as between subject factors. For the GLM of depression history, healthy controls with no history of depressive episodes (N = 95), ADHD patients with no history of depressive episodes (N = 43), and ADHD patients with one or more episodes in the past (N = 52) were added as between subject factors. Post-hoc analyses were performed using Fisher's least significant difference (LSD).

3. Results

3.1. Demographic, clinical and cognitive measures

Across the two groups, there were no significant differences in age of participants or in gender distribution. As expected, patients with ADHD scored significantly higher on ADHD symptom counts and significantly worse on cognitive measures, compared to the control group. The details are summarized in Table 1.

3.2. Between-group TBSS analysis of white matter microstructure

The whole-skeleton voxel-based between-group analysis with TBSS identified several clusters of decreased FA and increased MD and RD in the ADHD group when compared to the control group (Table 2, Fig. 1). No regions of increased FA or reduced MD or RD were observed, and no differences were observed for AD. For FA, differences between patients and controls were located in the body and splenium of the corpus callosum, anterior and superior corona radiata, posterior thalamic radiation, and tapetum. For MD and RD, overlapping regions were found, although case–control differences were even more widespread in both right en left hemisphere, also encompassing internal and external capsule, sagittal stratum, fornix, and SLF. The same pattern of results was observed when the analysis for FA was limited to the single scan acquisition protocol on which most scans were performed (N = 158; Supplementary Table 4).

AD and RD are derived from three quantitative indices (i.e. eigenvalues—λ1, λ2, λ3) that index tissue structure based on water molecule displacement. The first eigenvalue (λ1) measures AD, while RD is the average of the second (λ2) and third (λ3) eigenvalue. As a consequence, the signal-to-noise ratio of RD is sqrt(2) (the square root of 2) times higher than that of AD, which results in less power (through higher standard errors) to detect AD differences than RD differences. The absence of significant AD clusters in conjunction with positive RD clusters in our sample might thus have been due to power differences. In order to clarify this, we extracted mean AD and RD with standard errors from the significant between-group FA clusters. As expected, we found that the standard error for AD (3.14E − 06) was 1.27 times higher than the one for RD (2.46E − 06). The mean RD values significantly higher in the ADHD group compared to controls, ($F(1, 211) = 18.880$, $p = .00002$), while mean AD values were not ($F(1, 211) = .739$, $p = .391$). Furthermore, when we decomposed RD by extracting mean λ2 and λ3 from the significant between-group FA clusters and compared them between patients and controls, we found significant differences between patients and controls for both λ2 ($F(1, 211) = 18.901$, $p = .00002$) and λ3 ($F(1, 211) = 16.719$, $p = .00006$).

Table 2
Clusters showing significant differences in Fractional Anisotropy (FA), Mean Diffusivity (MD), and Radial Diffusivity (RD) between ADHD patients (N = 107) and healthy controls (N = 109).

Cluster	White matter tracts overlapping with the clusters (size of overlap in >10 voxels)[a]	Size (voxels)[b]	MNI coordinates (x;y;z)	Partial eta[2c]	p[d]
Clusters with significantly lower FA in ADHD patients					
1	Body and splenium of CC	453	−1;−26;23	.080	.042
2	Splenium of CC, SCR (R), PCR (R)	141	24;−35;28	.062	.046
3	Body of CC, SCR (R)	140	17;−24;33	.068	.040
4	Splenium of CC	56	16;−36;29	.055	.049
5	PCR (R)	32	18;7;34	.048	.049
6	PTR (R), Tapetum (R)	16	30;−51;15	.037	.049
Clusters with significantly higher MD in ADHD patients					
1	Body, splenium and genu of CC, EC (L + R), ACR (L + R), PCR (L + R), SCR (L), posterior limb of IC (L + R), retrolenticular part of IC (L + R), anterior limb of IC (L), sagittal stratum (R), cingulum, fornix (cres)/stria terminalis (L), CP (L), PTR (L + R), SFOF (L), fornix (cres)/Stria terminalis (R)	6763	37;−31;5	.153	.037
2	SLF (L)	407	−49;−38;12	.126	.042
3	EC (L)	40	−35;−9;−11	.086	.047
4	Sagittal stratum (L)	36	−42;−13;−15	.076	.048
5	Sagittal stratum (L)	16	−40;−23;−7	.059	.049
Clusters with significantly higher RD in ADHD patients					
1	Body, splenium and genu of CC, ACR (L + R), SCR (L + R), PCR (L + R), PTR (L + R), EC (L), retrolenticular part of IC (L + R), anterior limb of IC (L), posterior limb of IC (L + R), fornix (cres)/stria terminalis (L), sagittal stratum (L), SFOF (L), UF (L), SLF (L + R)	8411	2;−27;23	.133	.027
2	Sagittal stratum (R), EC (R), Fornix (cres)/Stria terminalis (R)	454	35;−13;−12	.099	.045
3	SLF (L)	386	−56;−24;5	.122	.044
4	SLF (L)	119	−18;28;30	.049	.048

CC corpus callosum, *ACR* anterior corona radiata, *FA* fractional anisotropy, *MD* mean diffusivity, *PCR* posterior corona radiata, *RD* radial anisotropy, *SCR* superior corona radiata, *RPIC* retrolenticular part of IC, *PTR* posterior thalamic radiation (include optic radiation), *PLIC* posterior limb of IC, *SLF* superior longitudinal fasciculus, *IC* internal capsule, *EC* external capsule, *SFOF* superior fronto-occipital fasciculus, and *UF* uncinate fasciculus.

[a] White matter tracts as defined with the Johns Hopkins University White Matter Label Atlas.

[b] Cluster size > 10 voxels.

[c] Partial eta squared based on mean FA, MD and RD of the cluster.

[d] P < .05, FWE-corrected, controlling for gender, age and scan acquisition protocol.

3.3. Association test of FA and MD with symptom scores in patients with ADHD

The whole-skeleton voxel-based regressions with TBSS in the patients showed that both ADHD symptom domains (inattention and hyperactivity/impulsivity) were not associated with FA or with MD. Furthermore, the partial correlation analyses of mean values of the significant between-group FA and MD clusters with either symptom domain did not show any significant correlations ($p_{adj} > .05$).

3.4. Association of FA and MD with cognitive measures in patients and controls

In the whole group, the partial correlation analyses showed that inhibition performance was negatively correlated with FA in cluster 4 ($r = -.265$; $p = .0001$), such that worse inhibition (i.e., more commission errors on the SART) was linked to lower FA. The delay discounting score was positively correlated with MD in cluster 1 ($r = .242$; $p = .0008$), such that steeper discounting on the Delay Discounting task (i.e., higher impulsivity) was linked to higher MD. To further explore which group contributed to the effects reported above, post-hoc analyses in the patients and in the control group separately revealed that the correlation with inhibition performance was predominantly present in the control group ($r = -.288$; $p = .004$) and did not reach significance in the ADHD patient group ($r = -.179$; $p = .099$). Steeper delay discounting was correlated with MD only in the ADHD patient group ($r = .283$; $p = .009$) and not among controls ($r = .032$; $p = .750$) (Fig. 2). There were no significant results for working memory or attentional performance (Table 3).

3.5. Effect of medication use and depression history on significant between-subject clusters of FA, MD, and RD

Sensitivity analyses were conducted to examine possible effects of stimulant medication use or depression history on significant clusters from the between-group analysis for FA, MD, and RD. Extracted mean values from the significant between-group clusters for FA, MD, and RD did not differ between medication-naive and stimulant-treated patients ($p > .05$) (Supplementary Table S2). There were no differences on the extracted mean values between ADHD patients with no history of depressive episodes and ADHD patients with one or more episodes in the past ($p > .05$) (Supplementary Table S3).

4. Discussion

In this study we examined white matter microstructure in adult patients with ADHD and healthy controls. Compared to the healthy individuals, patients with ADHD showed significantly reduced FA and increased MD and RD in several brain regions, but no differences in AD. While FA and MD differences were not related with symptom severity, lower FA in the splenium of the corpus callosum was associated with worse inhibition performance, and higher MD in several ROIs was associated with higher impulsivity.

Strongest effects were found in the body and splenium of the corpus callosum. This supports earlier reports that white matter anomalies in the corpus callosum are one of the most consistently found features in childhood ADHD (Cao et al., 2010; Pavuluri et al., 2009; Qiu et al., 2011; van Ewijk et al., 2014) and adult ADHD (Dramsdahl et al., 2012; Konrad et al., 2010), although some studies did not find corpus callosum abnormalities (de Zeeuw et al., 2012; Hamilton et al., 2008; Hong et al., 2014; Nagel et al., 2011; van Ewijk et al., 2012). Importantly, reduced FA

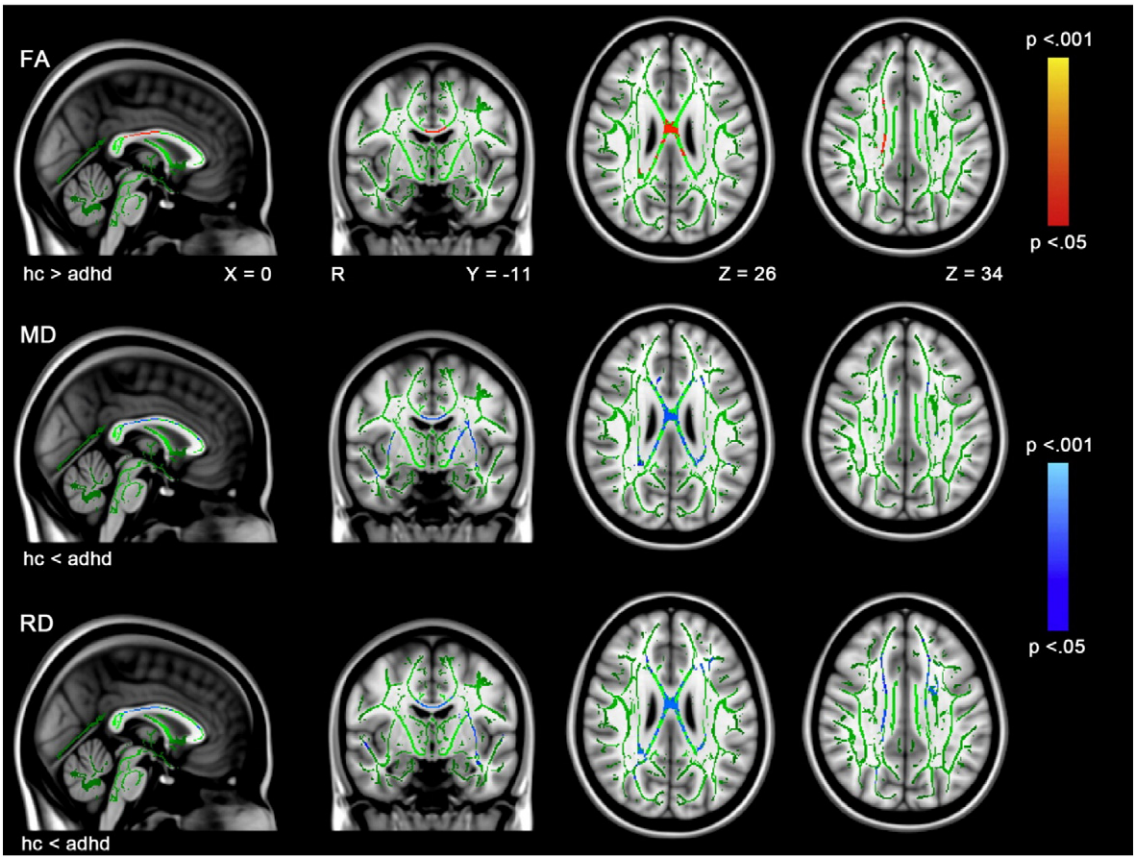

Fig. 1. Results from the tract-based spatial statistics (TBSS) analyses displayed on the MNI152 brain. Hot colors represent increased values, and cool colors represent decreased values. Decreased fractional anisotropy (FA), increased mean diffusivity (MD) and radial diffusivity (RD) are shown in individuals with ADHD compared to controls (threshold-free cluster enhancement, $p < .05$, corrected).

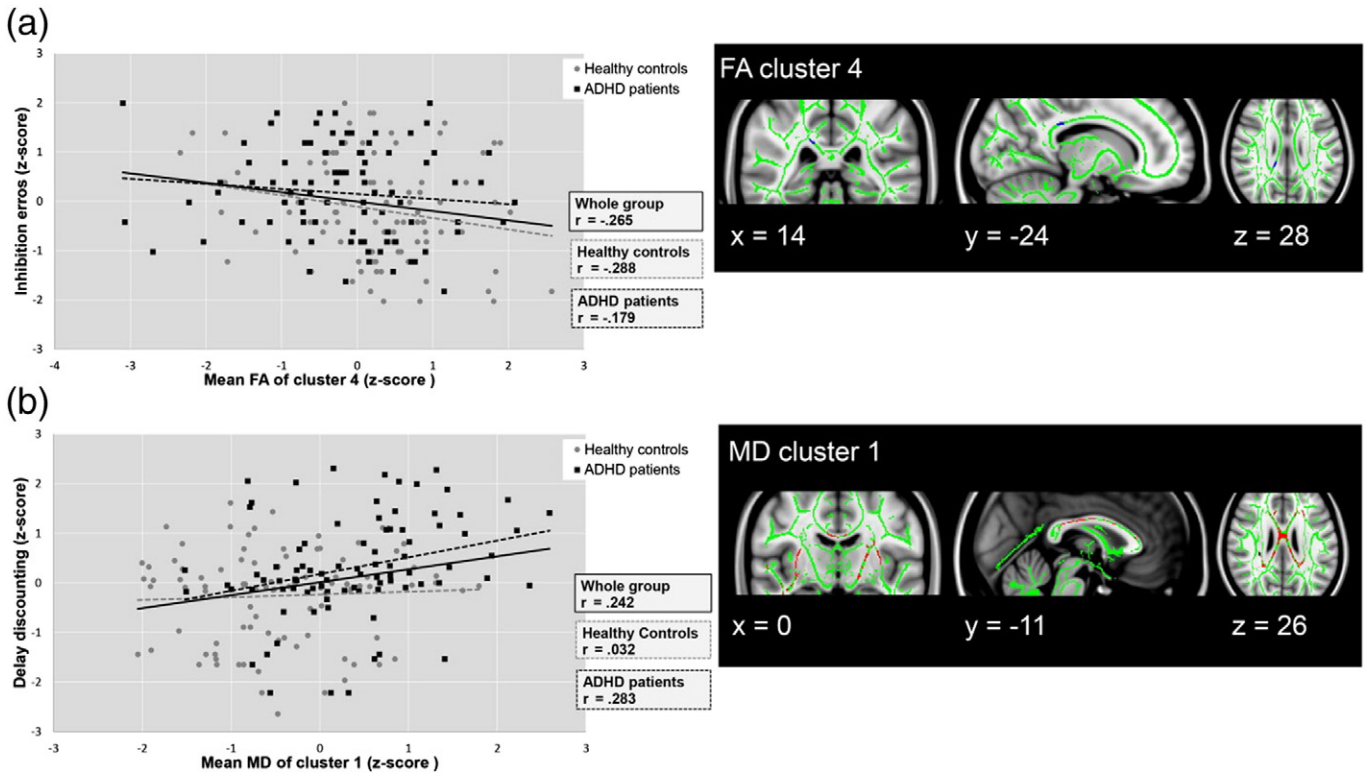

Fig. 2. Correlations between inhibition performance and mean FA in cluster 4 (a) and delay discounting score and mean MD in cluster 1 (b) for ADHD patients and controls separately; $^{*}p < .05$. Worse inhibition was reflected by a higher number of commission errors as measured with the Sustained Attention to Response Task (SART) task, and higher impulsivity was reflected by steeper discounting in the Delay Discounting task.

Table 3
Partial correlations between mean Fractional Anisotropy (FA) and Mean Diffusivity (MD) of between-subject clusters and cognitive measures controlling for age, gender, and scan protocol.

	Digit span[a]	SAD[b]	SART[c]	Delay discounting[d]
	109 HC/103 ADHD (N)	106 HC/100 ADHD (N)	100 HC/90 ADHD (N)	102 HC/88 ADHD (N)
FA cluster 1	.136*	−.105	−.223*	−.140
FA cluster 2	.039	−.127	−.068	−.051
FA cluster 3	−.066	−.090	−.036	−.133
FA cluster 4	.063	−.088	−.265**	−.213*
FA cluster 5	.1	−.054	−.101	−.043
FA cluster 6	.163*	−.018	−.054	−.175
MD cluster 1	−.054	.201*	.160*	.242**
MD cluster 2	−.063	.214*	.072	.121
MD cluster 3	−.108	.135	.094	.182*
MD cluster 4	−.099	.144*	.071	.142
MD cluster 5	−.033	.118	.033	.185*

* Indicates an uncorrected significance of $p < .05$.
** Indicates a corrected significance of $p < .001$.
[a] Digit Span raw backwards score (working memory).
[b] Errors Sustained Attention Dots (SAD) task (attention).
[c] Commission errors Sustained Attention to Response Task (SART) (inhibition).
[d] Score on Delay Discounting task (impulsivity).

values in the splenium were associated with worse inhibition performance. Poorer response inhibition in healthy children has been correlated previously with decreased FA (and increased MD) in the splenium (Paolozza et al., 2014). It has been linked to decreased splenium volume in children prenatally exposed to polychlorinated biphenyls (Stewart et al., 2003) and in adults with bipolar disorder (Bearden et al., 2011), populations also characterized by insufficient inhibitory control. The splenium of the corpus callosum connects interhemispheric somatosensory, auditory, occipital, and motor areas, which are important for visual object recognition and discrimination. Possibly, commission errors arise due to insufficient transmission of visual information to the brain areas executing inhibitory control. Our results show that the association between splenium FA and inhibition performance was weaker in patients than in healthy individuals, suggesting that this structure is less functional in ADHD patients.

Besides the corpus callosum, the observed differences in posterior and superior regions of the corona radiata are consistent with ADHD studies in childhood (Nagel et al., 2011; Qiu et al., 2011) and adulthood (Cortese et al., 2013). These regions are continuations of the posterior limb of the internal capsule to the sensorimotor cortex and contain axons primarily involved in low-level motor function. Alterations in these tracts might contribute to sensorimotor deficits in adult ADHD (Valera et al., 2010). Compared to controls, ADHD patients showed reduced FA in the posterior thalamic radiation consistent with an earlier finding in adult ADHD (Cortese et al., 2013), although a childhood study showed increased rather than decreased FA in this area (Peterson et al., 2011). The thalamic radiation contains fibres that run towards the occipital cortex carrying visual information and might be related to structural visual cortex abnormalities (Ahrendts et al., 2011) and functional visual deficits (Kim et al., 2014) in adult ADHD.

Our findings of increased MD suggest that white matter cellular density is lower in ADHD patients (Alexander et al., 2007). In agreement with earlier studies (de Luis-Garcia et al., 2015; Lawrence et al., 2013), these findings for MD were observed in more widespread areas of the brain than those for FA and our finds support a recent study that increased MD was correlated with worse performance indicators of ADHD (Conners Continuous Performance Test)(de Luis-Garcia et al., 2015).

Moreover, increased MD within a large cluster encompassing widespread regions was associated with steeper delay discounting. Steeper delay discounting occurs when smaller immediate rewards are preferred over larger delayed rewards, and is linked to impulsivity. Earlier studies found similarly that steeper delay discounting was associated with higher MD (and lower FA) in bilateral frontal/temporal lobes and in fronto-striatal tracts (Olson et al., 2009; Peper et al., 2013). A recent resting-state functional connectivity study in childhood ADHD showed that steeper delay discounting was related to differences in reward circuit connectivity (Costa Dias et al., 2013). In conclusion, aberrant structural and functional connectivity possibly influences the balanced interaction between the reward network and other cognitive control regions. This may unveil vulnerability to impulsive decision making in ADHD. Future research could benefit from using a connectomics approach, combined with multimodal imaging that includes diffusion measures as well as functional MRI (Hong et al., 2014; Shenton et al., 2014).

Decreased FA found in ADHD patients was driven by increases in RD rather than changes in AD. Although the biological correlates of those measures are not yet entirely clarified, it is believed that increases in RD (with minimal changes in AD) reflect decreased myelination, while decreases in AD reflect axonal damage or degeneration (Alexander et al., 2007; Song et al., 2002). Whereas studies in young children and adolescents with ADHD suggest delayed myelination (Nagel et al., 2011; Tamm et al., 2012), our results support the only other adult ADHD study that has investigated AD/RD and point to atypical myelination not only being delayed but rather representing a persistent anomaly in ADHD (Shaw et al., 2015). This implicates myelination as a novel target for genomic studies and for more tailored pharmacological treatment interventions.

We used two approaches to investigate effects of FA and MD on symptom severity. The first approach was a voxel-based regression with TBSS adapted from van Ewijk et al. (2014). The second approach was a conventional ROI analysis using the mean FA and MD of significant between-group clusters as predictors for symptoms. Both approaches yielded non-significant results, consistent with another adult ADHD study showing no association between corpus callosum differences and symptom severity (Dramsdahl et al., 2012). While this suggests that white matter differences in adult ADHD are independent of disease severity, a vast amount of literature does show relations with severity (Ashtari et al., 2005; Nagel et al., 2011; Shang et al., 2013; Shaw et al., 2015; van Ewijk et al., 2014). A firm conclusion on whether this can be explained by differences based on e.g. the age of the sample will have to await future analyses in larger samples. International collaboration in consortia like the Enabling Neuro Imaging Genetics through Meta-Analysis (ENIGMA) Consortium (www.ENIGMA.ini.usc.edu), which runs a ADHD working group, might provide increased power to clarify this point.

Our findings did not differ between drug-naïve ADHD patients and stimulant medicated patients which supports prior studies that found no confounding effects of (stimulant) medication (de Zeeuw et al.,

2012; Hamilton et al., 2008; van Ewijk et al., 2014). Additionally, our findings did not differ between ADHD patients with a history of major depression and ADHD patients without this comorbidity. Since deviant white matter integrity has also been found in numerous psychiatric disorders, it would be of particular interest to go across diagnostic boundaries in future studies and investigate whether certain white matter abnormalities are specific for ADHD or are shared between disorders.

While our DTI study sample is the largest one published to date for adult ADHD, it also has a limitation. We used two different diffusion scan acquisition protocols. However, this could not have biased our results, as group representation did not differ across protocols, and all analyses were performed with protocol as a covariate. Moreover, the same pattern of results held up when the main between-subject TBSS analysis for FA was limited to the single protocol on which most scans were performed, albeit with lower significance ($P_{FWE} = .10$) (see Supplementary Table S4). Additionally, we could not extensively study the role of comorbid substance abuse, which is an important concern considering the increased risk of substance use disorders in patients with ADHD (Gorzkowska et al., 2014; Wilens, 2004). Adolescent substance use has harmful effects on the development of white matter characteristics (Bava et al., 2013) and prefrontal cortex volume (Lejuez et al., 2010). Importantly, microstructural damage in corpus callosum has been suggested as a risk factor for alcohol use disorders (De Bellis et al., 2008).

In conclusion, this study demonstrates white matter microstructure alterations in adult ADHD and point to abnormal myelination. These white matter changes might represent a core trait of persistent ADHD that is independent of disease severity. The white matter microstructure alterations may have specific functional relevance given that lower FA in the corpus callosum was related to inhibition problems and increased MD in wide-spread tracts was related to impulsive decision making.

Conflict of interests

Cornelis C. Kan was a paid member of the European Adult ADHD Advisory Board of Eli Lilly in 2011 and 2012. Jan Buitelaar has served as a consultant, advisory board member, or speaker for Bristol-Myers Squibb, Janssen Cilag BV, Eli Lilly, Novartis, Schering-Plough, Shire, Servier, and UCB. He is not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, and royalties. Barbara Franke has received a speaker fee from Merz. The other authors report no financial relationships with commercial interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.pnpbp.2015.04.008.

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